Remarks/Arguments

The specification has been amended to include the required reference to the parent of the present continuation application. Prior to the present amendments, claims 1-43 were pending in this application. Claims 1-12, 18-20, 22-37, 39 and 41-43 were withdrawn from consideration. Claims 13-17, 21, 28 and 40 have been rejected. Claims 1-12, 18-37, 39 and 41-43 have been canceled, claims 13, 14, 15, 16 and 40 have been amended, and new claim 44 has been added. All amendments are fully supported by the specification as originally filed, and do not add new matter. Support for the recitation in claim 13 that the expression of the claimed polypeptide is induced by Wnt-1 is, for example, in Example 1, such as at page 54, lines 33-35. All amendments and cancellations were made without prejudice or disclaimer. Applicants explicitly reserve the right to claim any deleted subject matter in one or more continuing applications.

Election/Restrictions

Applicants note the finality of the restriction requirement. Accordingly, claims 1-12, 18-20, 22-37, 39, and 41-43 have been withdrawn from consideration and are now canceled.

Objections to the Specification

The specification has been objected to since it did not contain a reference to prior application Serial No. 09/182,562 filed on October 29, 1998, of which the present application is a continuation. The Examiner notes that, if a reference to the prior application was previously submitted within the time period set forth in 37 CFR 1.78(a), but not in the first sentence of the specification, and the priority benefit was recognized by the Office as shown by its inclusion on the first filing receipt, a petition under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) are not required.

The specification has been amended to indicate that the present application is a continuation of application Serial No. 09/182,562 filed on October 29, 1998, now abandoned. This priority claim was included in the Non-Provisional Application Transmittal under 37 CFR 1.53(b) filed on July 28,2003, and is included in the Filing Receipt mailed March 31,2004 and

the Corrected Filing Receipt mailed May 26, 2004. Accordingly, a petition under 35 CFR 1.78(a) is not required.

Claim Objections

Claims 13 and 15 have been objected to for depending from claims that are withdrawn from consideration. The current amendment of claims 13 and 15 is believed to obviate this objection.

Claim Rejections – 35 USC § 112

(1) Claims 14, 16 and 17 have been rejected under 35 USC 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regard as the invention.

In particular, claim 14 is held indefinite in its recitations of "human clone 65" and "mouse clone 65." The claim has been amended to include the appropriate SEQ ID NOS, which should obviate its rejection.

Claim 16 is held indefinite in its recitation of "clone 65 polypeptide." Claim 16 has been amended to refer to the polypeptides of claim 13, 14, 15, or 44, which, in turn, are characterized by reference to the appropriate SEQ ID NOS. Accordingly, the rejection of claim 16 and dependent claim 17 should also be withdrawn.

(2) Claims 13-17, 21, 38 and 40 were rejected under 35 USC 112, first paragraph, as allegedly failing to comply with the enablement requirement. The Examiner asserts that, although the specification discloses human and mouse clone 65 polypeptides of SEQ ID NO: 3 and SEQ ID NO: 6, respectively, and teaches "that it is believed that these protein [sic] are involved in the up-regulation of cancer genes,". . . "the specification provides no experimental evidence showing a correlation between clone 65 polypeptide expression and up-regulation of cancer genes." In addition, the Examiner refers to a post-filing date publication, Kirikoshi et al., *International Journal of Oncology* 20:777-783 (2002), as allegedly teaching that amounts of WRCH1 (clone 65 polypeptide) mRNA is lower in some cancer cell lines, but is either up-

regulated or down-regulated in other cases of primary tumors (Abstract). From this, the Examiner concludes that the clone 65 polypeptides "are not shown to have a clear role in cancer." The Examiner additionally refers to McClean and Hill, *Eur. J of Cancer*, 1993, vol. 29A, pp. 2243-2248, as allegedly teaching that p-glycoprotein can be overexpressed in CHO cells following exposure to radiation, without any concomitant overexpression of the p-glycoprotein mRNA, and takes this to mean that "changes in mRNA levels do not necessarily correlate with changes in protein levels." Another post-published paper, Saras et al., *Experimental Cell Research* 299:356-368, 2004, is cited in support of the notion that Wrch1 is "one of the least known Rho TGPases, and that its mechanism of action and regulation is not similar to the close related Cdc42-like GTPases, and that it has unusual properties.

The Examiner asserts that the utilities listed in the specification, including a diagnostic utility, "are neither substantial nor specific, because the specification fails to disclose a specific association between the expression levels of physiological functioning of clone 65 polypeptides and cancer or any other diseases," and adds that further research would be requirement to discover the association "between clone 65 expression levels of biological activity and cancer or any of the other name [sic] diseases," and such research would constitute undue experimentation.

Finally, the Examiner takes the position that even if there were enough teaching how to use a specific embodiment of a clone 65 polypeptide, the specification fails to teach how to use clone 65 polypeptide variants.

Accordingly, all claims are rejected for alleged lack of enablement for using the claimed polypeptides without undue experimentation.

Claim 21 has been canceled. The rejection of the remaining claims is respectfully traversed.

The present invention is based on the identification and isolation of a new member of the Rho protein family, designated clone 65. Human clone 65 shares around 59% sequence identity with CDC42, a well characterized member of the Rho family. Rho family proteins were known at the priority date of this application to contribute to the transforming actions of certain oncoproteins. For example, it was known that the Ras oncoproteins require Rho family protein

function to cause growth transformation, as stated on page 3, lines 29-32 of the application as filed. It was also known that aberrant activation of Rho family proteins can cause growth transformation, invasion, and metastasis in experimental models of carcinogenesis, which are responses typical of neoplasia (see, e.g. the passage bridging pages 3 and 4 of the specification).

However, prior to the present invention, no biological link between the Wnt-1 pathway and the Rho family genes in vertebrates had been identified. The data set forth Example 1 of the present application show that the mouse clone 65 encodes an intracellular protein that is strongly induced in the Wnt-1/C57mg cell line, but is absent, or at very low levels, in the parent C57mg cells. (Page 54, lines 33-35.) The fact that the clone 65 genes are Wnt-1 induced is further confirmed by the data set forth in Tao *et al., Genes & Development* 15:1796-1807 (2001) (copy enclosed), co-authored by the inventors of the present application. The data of Tao et al. demonstrate that Wrch-1 (clone 65) mRNA level increases in response to Wnt-1 signaling in Wnt-1 transformed cells (*"As shown in Figure 1A, Wrch-1 mRNA is up-regulated more than fourfold in C57MG/Wnt-1 cells versus C57MG/vector cells."* – page 1797, second column), Wnt-1 transgene induced mammary tumors, and Wnt-1 retrovirus infected cells. Based on these data, Tao et al. state: *"While mot members of the Rho family are constitutively expressed . . . , the expression of Wrch-1 is rapidly induced upon the activation of the Wnt-1 pathway. . . . Based on these results, Wrch-1 has the potential to mediate the effect of Wnt-1 on cell morphology and to contribute to the ability of Wnt-1 to transform cells and induce tumor formation."* (Page 1979, first column.) Evidence that Wrch-1 (clone 65) is a Wnt-1 responsive gene is also found in Taneyhill and Pennica, *BMC Developmental Biology* 2004, 4:6 (2004) (copy enclosed), co-authored by one of the inventors of the present application. As shown in Table I, the expression of the Wrch-1 gene increased 3.2-fold in Wnt-1 treated samples, and this gene has been confirmed to be truly Wnt-1 responsive. Claim 13 has been amended to reflect this by stating that the expression of the claimed polypeptides is induced by Wnt-1.

The Examiner notes that while the specification asserts that it is believed that the clone 65 proteins are involved in the up-regulation of cancer genes, "the specification provides no experimental evidence showing a correlation between clone 65 polypeptide expression and up-regulation of cancer genes." (Sentence bridging pages 4 and 5 of the Office Action.) Evidence confirming the teaching of the specification is provided in Tao *et al., supra*. Tao *et al.* show that

Wrch-1 (clone 65) can activate PAK-1 and JNK-1. PAK-1 is a p21-activated protein kinase that is known to promote cell motility and invasiveness, is overexpressed in 55% of human breast cancer and its expression has been shown to increase with progression of colorectal carcinomas to metastasis (Carter et al., *Clinical Cancer Research* 10:3448-3456 (2004). For a review of the role of PAK-1 and other PAK proteins see the attached review article by Kumar et al., *Nature Reviews/Cancer* 6:459-471 (2006). The review article specifically confirms that *"WNT1, which is a secreted morphogenic ligand with the ability to transform mammary epithelial cells, induces expression of the Rho GTPase WCH1, which is an activator of PAK1. The overexpression of WRCH1 alone can mimic WNT1-induced morphological phenotypes in transformed cells in a PAK1-dependent manner, which implicates PAK1 in the transformation of WNT1."* (Page 463, first column, citations omitted.) JNK-1 has been implicated in transformation and progression in numerous tumors including prostate cancer (Potapova et al., *Cancer Res.* 62:3257-3263 (2002) – copy enclosed); breast cancer (O'Hagan and Hassell, *Oncogene* 16:301-310 (1998) – copy enclosed) and lung cancer (Bost et al., *J. Biol. Chem.* 272:33422-33429 (1997) – copy enclosed). Accordingly, the results set forth in Tao *et al., supra* confirm that the clone 65 proteins are involved in the up-regulation of cancer genes, and that there is a correlation between clone 65 polypeptide expression and upregulation of cancer genes.

At page 38, lines 22-26, the specification states: *"It is contemplated that the clone 65 . . . polypeptides of the present invention may be used to treat various conditions, including those characterized by overexpression and/or activation of at least the Wnt pathway. Further, they are useful in diagnosing cancer, for example, as a marker for increased susceptibility to cancer or for having cancer."* The specification further teaches: *"Anti-clone 65 . . . polypeptide antibodies may . . . be useful in diagnostic assays for clone 65 . . . polypeptide, e.g. detecting its expression in specific cells, tissues, or serum. Thus, the antibodies may be used in the diagnosis of human malignancies (see, for example, U.S. Pat. No. 5,183,884)."* (Page 47, lines 28-31.) From the fact that the clone 65 gene is Wnt-induced, from the totality of the disclosure of the present application, including the above statements, and from the known role of Wnt-1 in tumorigenesis, one of ordinary skill in the art at the priority date of the present application would have readily understood and accepted that clone 65 is of use as a diagnostic indicator of cancers associated with the Wnt-1 pathway, such as those having aberrant Wnt-1 signaling.

Applicants strongly disagree with the Examiner's assertion that post-filing date publications do not show a clear role for the clone 65 polypeptides in cancer. Kirikoshi et al., cited in the Office Action, investigated the expression of Wrch-1 (clone 65) mRNA among certain cancer cell lines and primary tumors. While Wrch-1 mRNA is reported to be lower in human cancer cell lines and in some primary tumors than in normal cells, this does not undermine the teaching of the present invention. As discussed above, clone 65 is a Wnt-1 induced gene. Kirikoshi et al. provide no evidence that the cell lines and primary tumors investigated would involve the Wnt-1 pathway. Therefore, the results published in this paper provide no useful information about whether Wrch-1 (clone 65) is involved with and thus can be used in the diagnosis of cancers the pathogenesis of which involves the Wnt-1 pathway. The Examiner's attention is further directed to the review article by Kumar et al., discussed above, which clearly indicates the involvement of Wrch-1 in the regulation of cancer cells by PAK-1.

The assertion that "changes in mRNA levels do not necessarily correlate with changes in protein levels" (page 5 of the Office Action), as allegedly supported by McClean and Hill, is believed to be misplaced. As the Examiner will appreciate, the law does not require a "necessary" correlation between mRNA and protein levels in order to enable the use of a protein in the diagnosis of a disease, such as cancer. The proper legal standard is preponderance, i.e. only a showing that a correlation is more likely than not, is required. Enclosed is a Declaration by Dr. Randy Scott confirming that the expectation is that such correlation exists, and thus the proper legal standard is met. Dr. Scott holds a Ph.D. in biochemistry and has a distinguished career in the biotechnology industry, including the foundation of Incyte Pharmaceuticals, Inc., the world's first genomic information business. Dr. Scott is currently Chairman and Chief executive Officer of Genomic Health, Inc., a life science company conducting sophisticated genomic research to develop clinically validated molecular diagnostics, which provide individualized information on the likelihood of disease recurrence and response to certain types of therapy. Although part of his Declaration discusses the microarray technology, in paragraph 9 Dr. Scott states: *"Although there are some exceptions on an individual gene basis, it has been a consensus in the scientific community that elevated mRNA levels are good predictors of increased abundance of the corresponding translated proteins in a particular tissue. Therefore, diagnostic markers and drug candidates can be readily and efficiently screened and identified*

using this technique [i.e. the microarray technique which measures mRNA levels] *without the need to directly measure individual protein expression levels."* Accordingly, based on the gene expression data, one or ordinary skill would reasonably accept that it is more likely than not that the corresponding protein would also be present in cancer at elevated levels, relative to non-cancer cells.

The alleged teachings of Saras et al., i.e. that "Wrch-1 is one of the least known Rho GTPases," that "the mechanism of action and regulation of Wrch2 is not similar to the close related Cdc42 like GTPases, and that "it has unusual properties" (page 5 of the Office Action) are believed to have no bearing on the enablement of the invention claimed in the present application. As discussed above, the involvement of Wrch-2 (clone 65) in Wnt-1-associated cancers, as disclosed in the specification, has been confirmed and is well established. Saras et al. contains nothing that would contradict this.

In conclusion, the specification as filed fully enables the preparation and use of the clone 65 polypeptides the expression of which is induced by Wnt-1 in the diagnosis of cancer. Since Applicants argue enablement of the claims pending on the basis of the use of the clone 65 polypeptides in the diagnosis of Wnt-1-associated cancer, the Examiner's comments concerning therapeutic utility and not pertinent and will not be addressed in the present response.

In view of the foregoing arguments and evidence submitted with the present response, the Examiner is respectfully requested to reconsider and withdraw this rejection.

(3) Claims 13-17, 21, 38 and 40 were rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement. According to the rejection, "the specification fails to sufficiently describe the genus of polypeptides encompassed by the claims." (Page 9 of the Office Action.) The Examiner notes that Claims 14 and 16 are included in this rejection "because it is not clear if these claims are drawn to specific sequences or to a genus of sequences." In further support of the rejection, the Examiner points out that the mouse and human sequences are 93% homologous, and thus "the variation between the sequences disclosed does not appear t be as great as what is claimed." (Sentence bridging pages 8 and 9 of the Office Action.)

Claim 21 has been canceled. The rejection of the remaining claims is respectfully traversed.

Claim 13 has been amended to recite a 90% sequence identity to the murine or human clone 65 polypeptide sequences, coupled with the functional property that the expression of the claimed polypeptides is induced by Wnt-1. It is submitted that, in view of the known 93% sequence identity between the murine and human sequences and further in view of the functional recitation present in the genus claims, one of ordinary skill would reasonably accept that at the time this invention was made Applicants were in the possession of the invention within the full scope of claims currently pending. Claims 14 and 16 have been amended to recite the appropriate SEQ ID NOs, therefore their rejection is believed to be moot.

In view of the foregoing arguments, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Claim Rejections – 35 USC § 102

Claims 13, 14, 16, 21 and 38 were rejected under 35 USC 102(e) as allegedly being anticipated by Hillman (US 5,840,569). The Examiner noted that Hillman teaches a polypeptide that has an amino acid sequence that has greater than 97% sequence identity with SEQ ID NO: 3 from amino acid 63 to 242.

Even if the sequence identity were 100% with amino acids 63 to 242, the sequence identity calculated along the full length of the 258 amino acids long clone 65 polypeptide of SEQ ID NO: 3 would be less than 74%. Accordingly, Hillman does not anticipate any of the claims pending, and the present rejection should be withdrawn.

All claims pending in this application are believed to be in *prima facie* condition for allowance, and the early issuance of a Notice of Allowance is respectfully solicited.

Please charge any fees, including fees for extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39766-0157R1C1**).

Respectfully submitted,

Date: April 4, 2007

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